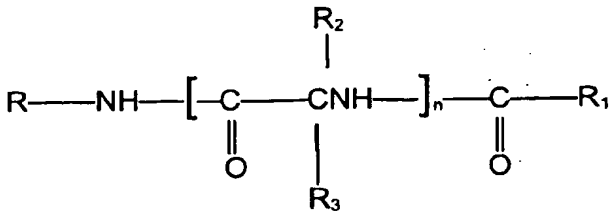
Claims

1. Use of a compound having the Formula (Ib)



Formula (Ib)

wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl or lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or/and at least one electron donating group;

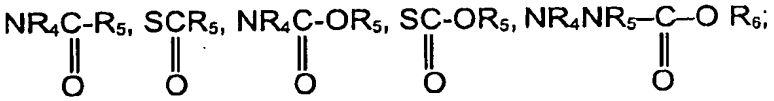
R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, lower alkyl heterocyclic, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with at least one electron donating group or/and at least one electron withdrawing group;

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or/and at least one electron donating group; and wherein heterocyclic in R_2 and R_3 is furyl, thienyl, pyrazolyl, pyrrolyl, methylpyrrolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl, piperazinyl, quinolyl,

triazolyl, tetrazolyl, isoquinolyl, benzofuryl, benzothienyl, morpholinyl, benzoxazolyl, tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl, pyrazolindinyl, imidazolinyl, imidazolindinyl, pyrrolidinyl, furazanyl, N-methylindolyl, methylfuryl, pyridazinyl, pyrimidinyl, pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl, azetidinyl or, when N is present in the heterocyclic, an N-oxide thereof;

Z is O, S, $S(O)_a$, NR_4, NR_6' or PR_4 or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic and Y may be unsubstituted or substituted with at least one electron donating group or/and at least one an electron withdrawing group, wherein heterocyclic has the same meaning as in R_2 or R_3 and, provided that when Y is halo, Z is a chemical bond, or ZY taken together is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, OPR_4R_5, PR_4OR_5, SNR_4R_7, NR_4SR_7, SPR_4R_5, PR_4SR_7, $NR_4PR_5R_6$, $PR_4NR_5R_7$, or $N^+R_5R_6R_7$,



R_6' is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl which may be unsubstituted or substituted with at least one electron withdrawing group or/and at least one electron donating group;

R_4, R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4, R_5 and R_6 may independently be unsubstituted or substituted with at least one electron withdrawing group or/and at least one electron donating group; and

R_7 is R_6 or $COOR_8$ or COR_8, which R_7 may be unsubstituted or substituted with at least one electron withdrawing group or/and at least one electron donating group;

R_8 is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with at least one electron withdrawing group or/and at least one electron donating group; and
n is 1-4; and
a is 1-3,

or of a pharmaceutically acceptable salt thereof,

for the preparation of a pharmaceutical composition useful for the prevention, alleviation or/and treatment of headache or/and painful conditions associated with or/and caused by cortical spreading depression (CSD).

2. Use according to claim 1, wherein wherein the headache is chronic headache.

3. Use according to claims 1 or 2, wherein the headache is migraine.

4. Use according to claim 3 for the manufacture of a medicament for the treatment of acute migraine.

5. Use according to any one of claims 1 to 4, wherein one of R_2 and R_3 is hydrogen.

6. Use according to any one of claims 1 to 5 wherein n is 1.

7. Use according to any one of claims 1 to 6 wherein at least one of R_2 and R_3 is hydrogen and n is 1.

8. Use according to any one of claims 1 to 7 wherein R is aryl lower alkyl and R_1 is lower alkyl.

9. Use according to any one of claims 1 to 8 wherein
R_2 and R_3 are independently hydrogen, lower alkyl, or ZY;
Z is O, NR_4 or PR_4;
Y is hydrogen or lower alkyl or
ZY is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, $NR_4C(=O)-R_5$ or $NR_4C(=O)-OR_5$.

10. Use according to claim 9 wherein R_2 is hydrogen and and R_3 is lower alkyl, or ZY;
Z is O, NR_4 or PR_4;
Y is hydrogen or lower alkyl;
ZY is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, $NR_4C(=O)-R_5$ or $NR_4C(=O)-OR_5$.

11. Use according to claim 9 wherein R_2 is hydrogen and R_3 is lower alkyl, which may be substituted or unsubstituted with at least one electron donating group or/and at least one electron withdrawing group, NR_4OR_5, or/and ONR_4R_7.

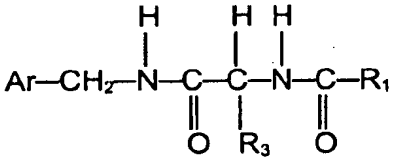
12. Use according to claim 9 wherein R_3 is lower alkyl which is unsubstituted or substituted with hydroxy or lower alkoxy, NR_4OR_5 or/and ONR_4R_7, wherein R_4, R_5 and R_7 are independently hydrogen or lower alkyl, R is aryl lower alkyl, which aryl group may be unsubstituted or substituted with at least one electron withdrawing group and R_1 is lower alkyl.

13. Use according to claim 12 wherein aryl is phenyl and is unsubstituted or substituted with halo.

14. Use according to any one of claims 1 to 13 wherein the compound is
(R)-2-acetamido-N-benzyl-3-methoxy-propionamide;
O-methyl-N-acetyl-D-serine-m-fluorobenzylamide;
O-methyl-N-acetyl-D-serine-p-fluorobenzylamide;

N-acetyl-D-phenylglycinebenzylamide;
D-1,2-(N, O-dimethylhydroxylamino)-2-acetamide acetic acid benzylamide;
D-1,2-(O-methylhydroxylamino)-2-acetamido acetic acid benzylamide.

15. Use of any one of claims 1 to 14 where in the compound has the Formula (IIb)



Formula (IIb)

wherein

Ar is phenyl which is unsubstituted or substituted with at least one halo group;

R_3 is CH_2-Q, wherein Q is lower alkoxy containing 1-3 carbon atoms and R_1 is lower alkyl containing 1-3 carbon atoms

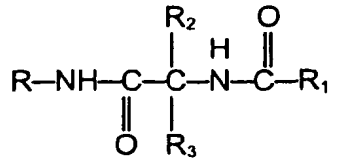
or of a pharmaceutically acceptable salt thereof.

16. Use according to claim 15 wherein Ar is unsubstituted phenyl.

17. Use according to claims 15 or 16 wherein halo is fluoro.

18. Use according to any one of claims 15 to 17 wherein R_3 is CH_2-Q, wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl.

19. Use of any one of claims 1 to 18, wherein the compound is in the R configuration having the formula



R

wherein

R is benyzl which is unsubstituted or substituted with at least one halo group;

R_3 is CH_2 -Q, wherein Q is lower alkoxy containing 1-3 carbon atoms and R_1 is methyl

or a pharmaceutically acceptable salt thereof.

20. Use according to claim 19 which is substantially enantiopure.

21. Use according to claims 19 or 20 wherein R is unsubstituted benzyl.

22. Use according to claims 19 to 21 wherein halo is fluoro.

23. Use according to claims 19 to 22 wherein R_3 is CH_2-Q, wherein Q is alkoxy containing 1-3 carbon atoms and R is unsubstituted benzyl.

24. Use according to any one of claims 1 to 4, wherein the compound of Formula (Ib) is (R)-2-Acetamido-N-benzyl-3-methoxypropionamide or a pharmaceutically acceptable salt thereof.

25. Use according to claim 24 wherein the compund is substantially enantiopure.

26. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for treatment with doses of the

compound of at least 100 mg/day, preferably of at least 200 mg/day, more preferably of at least 300 mg/day, most preferably of at least 400 mg/day.

27. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for treatment with doses of the compound of at a maximum 6 g/day, preferably of at a maximum 3 g/day, more preferably of at a maximum 1 g/day and most preferably of at a maximum 400 mg/day.

28. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for treatment with increasing daily doses until a predetermined daily dose is reached which is maintained during the further treatment.

29. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for treatment in three doses per day, preferably two doses per day, more preferably in a single dose per day.

30. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for an administration resulting in a plasma concentration of 7 to 8 µg/ml (trough) and 9 to 12 µg/ml (peak), calculated as an average over a plurality of treated subjects.

31. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for treatment for at least one week, preferably at least two weeks, more preferably at least four weeks, most preferably at least eight weeks.

32. Use according to any one of the preceding claims, wherein the pharmaceutical composition is prepared for oral administration.

33. Use according to any one of the preceding claims, wherein the pharmaceutical composition comprises a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders.

34. Use according to claim 33 wherein the pharmaceutical composition comprises a single dose form or comprises a separate dose form comprising a first composition comprising a compound as defined in any of the claims 1 and 5 to 25 and a second composition for the prevention, alleviation or/and the treatment of headache or/and CSD-associated disorders.

35. Use according to any one of the preceding claims wherein the pharmaceutical composition is prepared for administration in mammals.

36. Use according to claim 35 wherein the pharmaceutical composition is prepared for administration in humans.

37. A pharmaceutical composition comprising
(a) a compound as defined in any of the claims 1 and 5 to 25, and
(b) a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders.

38. The pharmaceutical composition according to claim 37 which is a single dose form or comprises a separate dose form comprising a first composition comprising a compound as defined in any of the claims 1 and 5 to 25 and a second composition for the prevention, alleviation or/and the treatment of headache or/and CSD-associated disorders.